## REMARKS/ARGUMENTS

Reconsideration of this Application and entry of this Amendment after Final are respectfully requested. This amendment and response are submitted with a Request for Continued Examination. The proposed amendment places the claims in better form for appeal. Additionally, this amendment addresses items brought up by the Examiner in the final office action. In view of the amendments and following remarks, favorable consideration and allowance of the application is respectfully requested.

Claims 1, 2, 5, 7 and 10-16 are pending in this application. Claims 1, 2 and 14 are canceled herein. Claims 12 and 13 have been amended to correct dependency. Claims 5, 10 and 15 have been amended to include the step of inhibiting the growth of *M. tuberculosis*. Support for this step is found in the specification in, *inter alia*, Examples 6 and 7. No new matter has been introduced as a result of the claim amendments.

By the amendments, Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

**Rejection Under USC §112**

Claims 1-2 have been rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. Claims 1 and 2 have been canceled.

**Rejection Under USC §102**

Claims 1-2 have been rejected under 35 USC §102(b) as being anticipated by Clifton et al. (WO 95/15940; PTO-892). Claims 1 and 2 have been canceled.

**Double Patenting**

Claims 1-2, 5, 7 and 10-16 have rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S.

Patent No. 6,013,660 in view of Griffith OW et al. Claims 1,2 and 14 have been canceled.

For the reasons discussed below, Applicants traverse the obviousness-type double patent rejection over U.S. Patent 6,013,660 (hereinafter "the '660 patent") in view of Griffith et al. As correctly characterized by the Examiner, the policy behind the judicially-created doctrine of obviousness-type double patenting is "to prevent the unjustified or improper timewise extension of the 'right to exclude' granted by a patent." The Applicants respectfully submit that allowance of the Applicants' pending claims 5, 7, 10-13 and 15-16 would clearly not lead to an improper timewise extension of the claims in the '660 patent.

As the focus of a double patenting rejection is, by definition, only the claims, Claim 1 of the '660 patent (the only independent claim) recites "[a] method for treating mammalian disease conditions associated with infection by pathogenic mycobacterium, said method comprising the steps of: administrating L-methionine-S-sulfoximine in a dose sufficient to significantly inhibit the growth or survival of the pathogenic mycobacterium without harming said mammal." (emphasis added) In the instant application, independent claims 5, 10 and 15 do not claim L-methionine-S-sulfoximine but rather other inhibitors of mycobacterial glutamine synthetase.

The Examiner states on page 8 of the instant application "[t]he '660 patent does not expressly disclose alpha alkylated L-methionine-S-sulfoximine or a racemic mixture of the same or other alpha alkylated butyrates for the treatment of pathogenic mycobacterium infection."

The disclosure of Griffith et al. cannot broaden the scope of claim 1 of the '660 patent because claim 1 recites only one inhibitor of mycobacterial glutamine synthetase, L-methionine-S-sulfoximine.

Thus, the methods recited in claims 1 and 2 of the '660 patent do not read on the methods recited in claims 5, 7, 10-13 and 15-16 of the instant application in view of the disclosure of Griffith et al. Moreover, the Applicants' claims are not just obvious

variations of claims 1 and 2 of the '660 patent that would extend the patent term of the '660 patent.

Applicants respectfully assert that claims 5, 7, 10-13 and 15-16 of the instant application are patentably distinct from claims 1 and 2 of the '660 patent because the claims are drawn to different chemical entities and the grant of a patent on claims 5, 7, 10-13 and 15-16 will not give rise to an extension of the patent rights granted in the '660 patent. Therefore, Applicants respectfully request the withdrawal of the double patenting rejection.

**Rejection Under USC §103**

To reject a claim under 35 USC §103(a), the Examiner bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. See *In re Bell*, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the Examiner cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. See *In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed Cir. 1992). In order to render a claim *prima facie* obvious, the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims, See *In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000).

Claims 1-2, 5, 7, 10-13, and 15-16 have been rejected under 35 USC §103(a) as being unpatentable over Harth et al. (J.Exp. Med.189(9), 1415-1435, 1999; in view of Griffith et al. (Methods in Enzymology, 143, 286-291). Claims 1 and 2 have been canceled. Applicants respectfully traverse the rejection of claims 5, 7, 10-13 and 15-16.

Harth teaches L-methionine-S-sulfoximine as an inhibitor of mycobacterial GS and its ability to block growth of pathogenic mycobacteria in human monocytes. Harth does not teach or suggest the alpha-alkylated compounds of formula 1. Griffith teaches alpha-ethyl-methionine-sulfoximine as an inhibitor of mammalian GS. Griffith does not teach or suggest inhibitors of mycobacterial GS or use of such inhibitors as anti-mycobacterial agents.

Amended independent claims 5, 10 and 15 are drawn to methods for treating, palliating or inhibiting mycobacterial injections by administering an anti-mycobacterial

composition and inhibiting the growth of a Mycobacteria species wherein the composition effectively inhibits Mycobacterial glutamine synthetase but does not substantially inhibit mammalian glutamine synthetase at an anti-mycobacterial effective amount.

Neither Harth nor Griffiths, either alone or in combination, teach or suggest anti-mycobacterial compositions that inhibit the growth of a Mycobacteria species.

Furthermore, the Examiner points to page 1434, column 1, paragraph 5, line 13 to column 2, paragraph 1, lines 1-6 of Harth which states "[h]ence, drugs functionally analogous to L-methionine-S-sulfoximine, but perhaps with even greater specificity for *M. tuberculosis* enzyme relative to the mammalian enzyme have great potential as antibiotics against this pathogen." However, Harth does not teach or suggest any such compounds. Furthermore, on page 1429, column 1 paragraph 2, lines 5-9, Harth states that of the four racemic forms of DL-methionine-SR-sulfoximine, only L-methionine-S-sulfoximine is active against glutamine synthetase. Therefore, it is not obvious that related drugs will function in the desired manner.

As stated in the Office Action on page 14, "Harth et al. does not expressly disclose the use of the particular α-alkylated compounds of formula 1 with methyl or ethyl substitutions at the R-1 position for inhibiting, treating or palliating mycobacterial infections; in particular Harth et al. does not disclose the use of alpha-methyl-(D or L)-methionine-(S or R)-sulfoximine or alpha-methyl-L-methionine-S-sulfoximine or alpha-ethyl-L-methionine-S-sulfoximine as anti-mycobacterial agents."

At the time of invention of the instant claims, it was not known if the established inhibitors of mammalian GS would also inhibit mycobacterial GS. Applicant respectfully points out that the glutamine synthetase (GS) used in Griffith et al. is mammalian GS which is a different protein than mycobacterial GS. As is known to persons of ordinary skill in the art, mycobacterial GS are dodecamers comprised of two face-to-face hexameric rings of subunits and are regulated by adenylation. Mammalian GS are octamers rather than dodecamers, are of lower molecular weight, and are not regulated by adenylation. The properties and regulation of mammalian GS and mycobacterial GS

are therefore different and variable and a person of ordinary skill in the art would recognize that their susceptibility to inhibitors can vary significantly. Applicants draw the examiner's attention to paragraphs 0038 and 0039 of the instant specification for a discussion of the differences between mammalian GS and mycobacterial GS. Therefore, alpha-alkylated methionine sulfoximines were not known to even inhibit mycobacterial GS and certainly not known to cause selective inhibition of mycobacterial GS *in vivo* or to inhibit growth of Mycobacteria before the invention recited in the instant claims.

Furthermore, regulation of mammalian GS and mycobacterial GS are different and variable and a person of ordinary skill in the art would recognize that their susceptibility to inhibitors can vary significantly. Therefore until the instant invention, it was not known if these claimed compounds would exhibit inhibition of mycobacterial GS to a degree sufficiently greater than their inhibition of mammalian GS. Furthermore, it was not recognized that a compound with preferentially higher inhibitory activity for mycobacterial GS over mammalian GS would be preferential for inhibiting mycobacterial growth *in vivo* and useful in the treatment, palliation and/or inhibition of mycobacterial infections.

In view of the foregoing, Applicant respectfully submits that Griffith and Harth, either alone or in combination, do not teach or suggest all the elements of the instant claims, namely methods of treating mycobacterial infections using the compounds of formula 1 wherein the composition effectively inhibits mycobacterial GS but does not substantially inhibit mammalian GS and growth of a Mycobacteria species is inhibited. Furthermore, there is no expectation of success since it has been established in the prior art that mammalian GS and mycobacterial GS are substantially different proteins and compounds that have inhibitory effects on mammalian GS do not necessarily inhibit mycobacterial GS. Therefore Applicants respectfully submit that the Examiner cannot establish *prima facie* obviousness of claims 5, 7, 10-13 and 15-16. Accordingly, Applicant respectfully submits that claims 5, 7, 10-13 and 15-16 are not obvious under 35 USC §103(a) over Harth et al. in view of Griffith et al. and requests the withdrawal of the outstanding rejection on this basis.

Claim 14 has been rejected under 35 USC §103(a) as being unpatentable over Anderson ME (Chemico-Biological Interactions, 111-112, 1998; 1-14), in view of Harth et al. Claim 14 has been canceled.

**Conclusion**

Applicants respectfully assert that the pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

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